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NEWS 26
         NOV 19
              19 SEPTEMBER 2007: CURRENT WINDOWS VERSION IS V8.2,
NEWS EXPRESS
              CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
              AND CURRENT DISCOVER FILE IS DATED 19 SEPTEMBER 2007.
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=> file casreact
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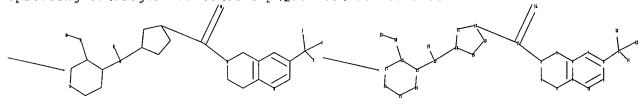
FILE CONTENT: 1840 - 17 Nov 2007 VOL 147 ISS 22

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chain nodes : 11 12 13 14 15 16 22 29 30 ring nodes : 2 3 4 5 6 7 8 9 10 17 18 19 20 21 23 chain bonds : 2-15 8-11 11-12 11-13 11-14 15-16 15-17 20-22 22-23 22-29 28-30 30-31 ring bonds : 3-4 4-5 4-7 5-6 5-10 7-8 8-9 9-10 17-18 17-21 18-19 19-20 1-2 1-6 2-3 20-21 23-24 23-28 24-25 25-26 26-27 27-28 exact/norm bonds : 1-2 1-6 2-3 2-15 3-4 5-6 15-16 20-22 22-23 28-30 exact bonds : 8-11 11-12 11-13 11-14 15-17 17-18 17-21 18-19 19-20 20-21 22-29 23-24 23-28 24-25 25-26 26-27 27-28 30-31

normalized bonds :

4-5 4-7 5-10 7-8 8-9 9-10

isolated ring systems : containing 1:17:23:

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:Atom 18:Atom 19:Atom 20:Atom 21:Atom 22:CLASS 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom 29:CLASS 30:CLASS 31:CLASS fragments assigned product role:

containing 1

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L1 HAS NO ANSWERS L1STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.

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FULL SEARCH INITIATED 08:37:08 FILE 'CASREACT'

SCREENING COMPLETE - . . 556 REACTIONS TO VERIFY FROM 3 DOCUMENTS

100.0% DONE 556 VERIFIED 131 HIT RXNS 2 DOCS

SEARCH TIME: 00.00.02

L2 2 SEA SSS FUL L1 (131 REACTIONS)

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ANSWER 1 OF 2 CASREACT COPYRIGHT 2007 ACS on STN

142:482029 CASREACT ACCESSION NUMBER:

TITLE: Preparation of [(1R,3S)-3-isopropyl-3-[[3-

> (trifluoromethyl) -7, 8-dihydro-1, 6-naphthyridin-6(5H) yl]carbonyl]cyclopentyl][(3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl]amine salt as chemokine receptor CCR-2

antagonist

Cai, Dongwei; Fleitz, Fred; Ge, Min; Hoerrner, Scott; INVENTOR(S):

> Javadi, Gary; Jensen, Mark; Larsen, Robert; Li, Wenjie; Nelson, Dorian; Szumigala, Elizabeth; Yang,

Lihu; Zhou, Changyou

PATENT ASSIGNEE(S): Merck & Co., Inc., USA SOURCE: PCT Int. Appl., 33 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE WO 2004-US35294 20041025 A1 20050519 WO 2005044795

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PRIORITY APPLN. INFO.:
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OTHER SOURCE(S):

MARPAT 142:482029

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R YIELD 99%

RX(4) RCT N 625097-29-2 RGT S 1333-74-0 H2 PRO R 624733-88-6 GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention provides an efficient synthesis for the preparation of [(1R,3S)-3-isopropyl-3-[[3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl]carbonyl]cyclopentyl][(3S,4S)-3-methoxytetrahydro-2H-pyran-4yl]amine (I) and its succinate salt. The present invention addnl. provides an efficient syntheses for the preparation of intermediates, i.e. (3R) -3-methoxytetrahydro-4H-pyran-4-one (II), (1S; 4S) -4-(2, 5-dimethyl-1Hpyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid (III), and 3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (IV), and for the preparation of the precursor (3S, 4S) - N - ((1S, 4S) - 4 - isopropyl - 4 - [[3 - isopropyl - 4 - isopropyl(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl]carbonyl]cyclopent-2-en-1-yl)-3-methoxytetrahydro-2H-pyran-4-amine (V). The invention addnl. resides in the superior properties of the I succinate. Thus, 730 g III was treated with 228 mL methanesulfonyl chloride in the presence of 0.93 L diisopropylethylamine in 6.6 L THF at 0-13°, stirred at room temperature for 4 h, cooled to .apprx.15°, treated with IV.HCl, warmed to 23°, treated with 0.93 L diisopropylethylamine with cooling at .apprx.25° over 15 min, and aged for .apprx.1 h to give 1.055 kg the compound (VI). VI (1.055 kg) in MeOH was added to 1 kg hydroxylamine hydrochloride, 50% aqueous hydroxylamine (1 L), and 5 L H2O, and the resulting slurry was refluxed at 71° for 6 h to give, after treatment with anhydrous HCl in isopropanol, the amine dihydrochloride (VII) (0.76 kg). VII (777 g) was slurried in 3 L iso-Pr acetate and the mixture was cooled in an ice bath, successively treated with 860 mL n-Bu3N, 260 mL isopropanol, and sodium triacetoxyborohydride (724 g, at 5°), and after 1 h, treated with a solution of II in iso-Pr acetate (1.76 L of a 160 g/L solution), and allowed to react for 6 h to give 654 g crude V (90%). V (640 g) was diluted with 6.4 L MeOH, charged to an autoclave, treated with a slurry of 256 g 5% Pd-C in 5.0 L MeOH, and hydrogenated under H pressure of 40 psi at 25° overnight to give a solution of 633 g I in MeOH (98.5%) which was concentrated to an oil (770 g). The oil was dissolved in 3.1 L iso-Pr acetate and the solution was concentrated to a brown oil. Dilution with iso-Pr acetate and

concentration was repeated two addnl. times. The resulting oil was converted into I benzenesulfonate (1.645 kg) by treating with 283 g benzenesulfonic acid in iso-Pr acetate and treatment with heptane and the resulting benzenesulfonate salt was treated with a mixture of K2CO3, H2O, and iso-Pr acetate to give an oil containing 1.16 kg I. The latter oil was treated with 294 g succinic acid in ethanol and heptane to give 1.328 kg I succinate.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 2 OF 2 CASREACT COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 142:482028 CASREACT

TITLE: Preparation of [(1R,3S)-3-isopropyl-3-[[3-

(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)yl]carbonyl]cyclopentyl][(3S,4S)-3-methoxytetrahydro2H-pyran-4-yl]amine salt as chemokine receptor CCR-2

antagonist

INVENTOR(S): Jensen, Mark; Larsen, Robert; Sidler, Daniel Richard

PATENT ASSIGNEE(S): Merck & Co., Inc., USA SOURCE: PCT Int. Appl., 28 pp.

CODEN. DIVVD3

CODEN: PIXXD2

DOCUMENT TYPE: Patent

English

LANGUAGE: Er FAMILY ACC. NUM. COUNT: 1 PATENT INFORMATION:

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RX(3) OF 92 ...N ===> O...

N

O YIELD 99%

GI

RX(3)

RCT N 625097-29-2

RGT P 1333-74-0 H2

PRO O 624733-88-6

CAT 7440-05-3 Pd

SOL 67-56-1 MeOH

CON 18 hours, 25 deg C, 40 psi

NTE Pd adsorbed on carbon used as catalyst, reaction carried out in autoclave, industrial manufacture

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

The present invention provides an efficient synthesis for the preparation of [(1R,3S)-3-isopropyl-3-[[3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-y1]carbony1]cyclopenty1][(3S,4S)-3-methoxytetrahydro-2H-pyran-4yl]amine (I) and its succinate salt. The present invention addnl. provides an efficient syntheses for the preparation of intermediates, i.e. (3R) -3-methoxytetrahydro-4H-pyran-4-one (II), (1S, 4S) -4-(2, 5-dimethyl-1Hpyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid (III), and 3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (IV), and for the preparation of the precursor (3S,4S)-N-((1S,4S)-4-isopropyl-4-[[3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl]carbonyl]cyclopent-2-en-1-y1)-3-methoxytetrahydro-2H-pyran-4-amine (V). The invention addnl. resides in the superior properties of the I succinate. I succinate is useful for treating, ameliorating, controlling or reducing the risk of an inflammatory and immunoregulatory disorder or disease or rheumatoid arthritis. Thus, 730 q III was treated with 228 mL methanesulfonyl chloride in the presence of 0.93 L diisopropylethylamine in 6.6 L THF at 0-13°, stirred at room temperature for 4 h, cooled to .apprx.15°, treated with IV.HCl, warmed to 23°, treated with 0.93 L diisopropylethylamine with cooling at .apprx.25° over 15 min, and aged for .apprx.1 h to give 1.055 kg the compound (VI). VI (1.055 kg) in MeOH was added to 1 kg hydroxylamine hydrochloride, 50% aqueous hydroxylamine (1 L), and 5 L H2O, and the resulting slurry was refluxed at 71° for 6 h to give, after treatment with anhydrous HCl in isopropanol, the amine dihydrochloride (VII) (0.76 kg). VII (777 g) was slurried in 3 L iso-Pr acetate and the mixture was cooled in an ice bath, successively treated with 860 mL n-Bu3N, 260 mL isopropanol, and sodium triacetoxyborohydride (724 g, at 5°), and after 1 h, treated with a solution of II in iso-Pr acetate (1.76 L of a 160 g/L solution), and allowed to react for 6 h to give 654 g crude V (90%). V (640 g) was diluted with 6.4 L MeOH, charged to an autoclave, treated with a slurry of 256 q 5% Pd-C in 5.0 L MeOH, and hydrogenated under H pressure of 40 psi at 25° overnight to give a solution of 633 g I in MeOH (98.5%) which was concentrated to an oil (770 g).

The

oil was dissolved in 3.1 L iso-Pr acetate and the solution was concentrated to

brown oil. Dilution with iso-Pr acetate and concentration was repeated two ${\tt addnl.}$

times. The resulting oil was converted into I benzenesulfonate (1.645 kg) by treating with 283 g benzenesulfonic acid in iso-Pr acetate and treatment with heptane and the resulting benzenesulfonate salt was treated with a mixture of K2CO3, H2O, and iso-Pr acetate to give an oil containing 1.16 kg I. The latter oil was treated with 294 g succinic acid in ethanol and heptane to give 1.328 kg I succinate.

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=> d his

(FILE 'HOME' ENTERED AT 08:36:33 ON 20 NOV 2007)

1

FILE 'CASREACT' ENTERED AT 08:36:46 ON 20 NOV 2007

L1 STRUCTURE UPLOADED

L2 2 S L1 FULL

=> log y
COST IN U.S. DOLLARS
FULL ESTIMATED COST

SINCE FILE TOTAL ENTRY SESSION 123.84 124.05

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE TOTAL ENTRY SESSION

CA SUBSCRIBER PRICE

-1.46

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PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

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      2
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NEWS
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                 CHEMCATS accession numbers revised
NEWS
         JUL 02
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NEWS
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         JUL 16
NEWS
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NEWS 10
                 CAS REGISTRY enhanced with new experimental property tags
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NEWS 11
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NEWS 12
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                 patent family display formats from INPADOCDB
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NEWS 19
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NEWS 24
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                 Derwent Indian patent publication number format enhanced
NEWS 26
         NOV 19
                 WPIX enhanced with XML display format
NEWS EXPRESS
              19 SEPTEMBER 2007: CURRENT WINDOWS VERSION IS V8.2,
              CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
              AND CURRENT DISCOVER FILE IS DATED 19 SEPTEMBER 2007.
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COST IN U.S. DOLLARS

SINCE FILE TOTAL ENTRY SESSION 0.21 0.21

FULL ESTIMATED COST

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STRUCTURE FILE UPDATES: 19 NOV 2007 HIGHEST RN 954997-95-6 DICTIONARY FILE UPDATES: 19 NOV 2007 HIGHEST RN 954997-95-6

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chain nodes : 11 12 13 14 15 16 22 ring nodes : 9 10 17 18 19 20 21 23 24 25 26 chain bonds : 2-15 8-11 11-12 11-13 11-14 15-16 15-17 20-22 22-23 22-29 28-30 ring bonds : 4-5 4-7 5-6 5-10 7-8 8-9 9-10 1-2 1-6 2-3 3-4 17-18 17-21 18-19 19-20 23-24 23-28 24-25 25-26 26-27 20-21 exact/norm bonds : 1-2 1-6 2-3 2-15 3-4 5-6 15-16 20-22 22-23 28-30 exact bonds : 8-11 11-12 11-13 11-14 15-17 17-18 17-21 $\cdot 18-19$ 19-20 20-21 22-29 23-2423-28 24-25 25-26 26-27 27-28 30-31

normalized bonds :

4-5 4-7 5-10 7-8 8-9 9-10

isolated ring systems : containing 1 : 17 : 23 :

Match level :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:Atom 18:Atom 19:Atom 20:Atom 21:Atom 22:CLASS 23:Atom 24:Atom 25:Atom 26:Atom 27:Atom 28:Atom 29:CLASS 30:CLASS 31:CLASS

L1STRUCTURE UPLOADED

=> d 11

L1 HAS NO ANSWERS

L1STR

Structure attributes must be viewed using STN Express query preparation.

SAMPLE SEARCH INITIATED 08:32:16 FILE 'REGISTRY' SAMPLE SCREEN SEARCH COMPLETED -13 TO ITERATE

100.0% PROCESSED 13 ITERATIONS 6 ANSWERS

SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE** BATCH **COMPLETE**

PROJECTED ITERATIONS: 44 TO 476 PROJECTED ANSWERS: 6 TO 266

L26 SEA SSS SAM L1

=> s l1 full

FULL SEARCH INITIATED 08:32:21 FILE 'REGISTRY' FULL SCREEN SEARCH COMPLETED - 241 TO ITERATE

100.0% PROCESSED 241 ITERATIONS 84 ANSWERS

SEARCH TIME: 00.00.01

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COST IN U.S. DOLLARS

SINCE FILE TOTAL ENTRY SESSION 172.10 172.31

FULL ESTIMATED COST

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=> s 13/prep full

8 L3

4491967 PREP/RL

7 L3/PREP

(L3 (L) PREP/RL)

=> d ibib abs hitstr tot

ANSWER 1 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2006:121960 CAPLUS

DOCUMENT NUMBER:

144:212759

TITLE:

Preparation of tetrahydropyranylaminocyclopentylcarbon

yltetrahydropyridopyridines as modulators of CCR2

chemokine receptor activity.

INVENTOR(S):

Demartino, Julie; Akiyama, Taro; Struthers, Mary; Yang, Lihu; Berger, Joel P.; Morriello, Gregori; Pastemak, Alexander; Zhou, Changyou; Mills, Sander G.; Butora, Gabor; Kothandaraman, Shankaran; Guiadeen, Deodialsingh; Tang, Cheng; Jiao, Richard; Goble,

Stephen D.; Moyes, Christopher

PATENT ASSIGNEE(S):

SOURCE:

U.S. Pat. Appl. Publ., 84 pp., Cont.-in-part of Ser.

No. US 2004-923594, filed on 20 Aug 2004

whichCont.-in-pa

CODEN: USXXCO

DOCUMENT TYPE:

Patent English

USA

LANGUAGE:

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006030582 US 2004167156	A1 A1	20060209	US 2005-102417 US 2003-425167	20050408

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US 6812234
                          B2
                                20041102
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                          Α1
                                20050519
                                                                    20040820
    US 7230008
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    EP 1627636
                          A1
                                20060222
                                            EP 2005-270011
                                                                    20050418
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             BA, HR, IS, YU
                                            US 2002-376180P
                                                                P 20020429
PRIORITY APPLN. INFO.:
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                                            US 2003-425167
                                                                A2 20040820
                                            US 2004-923594
                                                                P
                                                                   20020429
                                            US 2002-376291P
                                            US 2005-102417
                                                                A 20050408
OTHER SOURCE(S):
                         MARPAT 144:212759
GΙ
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$$R^9$$
 X
 R^{10}
 R^{10}

AΒ Title compds. [I; X = O, NR20, S, SO, SO2, CR21R22, NSO2R20, NCOR20, CO, etc.; R20 = H, (substituted) alkyl, Ph, PhCH2, cycloalkyl; R21, R22 = H, OH, (substituted) alkyl, alkoxy, Ph, PhCH2, cycloalkyl; R1 = (substituted) alkyl, alkoxyalkyl, alkylthioalkyl, heterocyclyl, cyano, Ph, CO2R20, NHCOR20, etc.; R2 = H, OH, halo, CO2R20, (substituted) alkyl, etc.; R3 = O, null; R4 = H, alkyl, CF3, OCF3, Cl, F, Br, Ph; R5 = (substituted)alkyl, alkoxy, alkylcarbonyl, Ph, PhO, pyridyl, CO2R20, etc.; R6 = H, alkyl, CF3, F, Cl, Br; R7 = H, (substituted) alkyl; R8 = H, F, OH, cycloalkyloxy, (substituted) alkyl, CO2R20, etc.; R9 = H, OH, (substituted) alkyl, alkoxy, CO2R20; R8R9 = atoms to form a 3-6 membered ring; R10 = H, F, cycloalkoxy, (substituted) alkyl; R8R10 = atoms to form a 6-8 membered ring; n = 0-2; dashed line = optional double bond], were prepared Thus, title compound (II) was prepared in many steps. I generally showed IC50 values of $<1 \mu M$ in a CCR-2 receptor binding assay. ΙT 625097-14-5P 625097-40-7P 625097-89-4P RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of tetrahydropyranylaminocyclopentylcarbonyltetrahydropyridopyr idines as modulators of CCR2 chemokine receptor activity) 625097-14-5 CAPLUS RN Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-CN (trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1methylethyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

RN 625097-40-7 CAPLUS

CN Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-1-oxido-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 625097-89-4 CAPLUS

CN Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3R)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(3,3,3-trifluoropropyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 851983-90-9 CAPLUS

CN Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(2,2,2trifluoroethyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

ANSWER 2 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:431408 CAPLUS

DOCUMENT NUMBER: 142:482030

TITLE: Tetrahydropyranyl cyclopentyl tetrahydropyridopyridine

modulators of chemokine receptor activity

Jiao, Richard; Butora, Gabor; Goble, Stephen D.; INVENTOR(S):

Guiadeen, Deodialsingh; Mills, Sander G.; Morriello, Gregori; Pasternak, Alexander; Tang, Cheng; Yang,

Lihu; Zhou, Changyou; Kothandaraman, Shankaran; Moyes,

Christopher

PATENT ASSIGNEE(S): USA

U.S. Pat. Appl. Publ., 86 pp., Cont.-in-part of U.S. SOURCE:

Ser. No. 425,167.

CODEN: USXXCO

DOCUMENT TYPE:

Patent English LANGUAGE:

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATE	ENT NO.	KIND DATE					APPL	ICAT	ION		DATE					
	20051074	22		A1 20050519 B2 20070612					US 2	004-	9235	94		2	0040	320
US 2	20041671	56		A1 B2			0826		US 2	003-	4251	67		2	0030	429
US 2	20060305	82		A1 A1		2006	0209			005-1		20050408 20050418				
		BE,	•	DE,	DK,	ES,	FR,	GB,	GR,	IT,	LI,	LU,		SE,	MC,	PT,
PRIORITY	BA,	HR,	IS,		,	1.0,	1111,		•	002-		•			0020	
INIONIII	TILL DIV.	11110.	•						US 2	002-	3762	91P	:	_	0020	429
									US 2	004-	9235	94	Ž	A2 2		320

OTHER SOURCE(S):

MARPAT 142:482030

GΙ

The present invention is directed to methods for treating, preventing, ameliorating, controlling or reducing the risk of an inflammatory or immunoregulatory disorder or disease, which method comprises the administration to a patient of an effective amount of the title compds. which are useful as modulators of chemokine receptor activity. In particular, these compds. are useful as modulators of the chemokine receptor CCR-2. E.g., I was prepared by reaction of the synthesized intermediate II with tetrahydro-4H-pyran-4-one in the presence of Na triacetoxyborohydride.

IT 625097-14-5P 625097-40-7P 625097-89-4P

851983-90-9P

RL: SPN (Synthetic preparation); PREP (Preparation) (tetrahydropyranyl cyclopentyl tetrahydropyridopyridine modulators of chemokine receptor activity)

RN 625097-14-5 CAPLUS

CN Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 625097-40-7 CAPLUS

CN Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-1-oxido-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

RN 625097-89-4 CAPLUS

CN Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3R)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(3,3,3-trifluoropropyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 851983-90-9 CAPLUS

CN Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(2,2,2-trifluoroethyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT:

THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Preparation of [(1R,3S)-3-isopropyl-3-[[3-

(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)yl]carbonyl]cyclopentyl][(3S,4S)-3-methoxytetrahydro2H-pyran-4-yl]amine salt as chemokine receptor CCR-2

antagonist

Cai, Dongwei; Fleitz, Fred; Ge, Min; Hoerrner, Scott; Javadi, Gary; Jensen, Mark; Larsen, Robert; Li, INVENTOR(S):

Wenjie; Nelson, Dorian; Szumigala, Elizabeth; Yang,

Lihu; Zhou, Changyou

PATENT ASSIGNEE(S):

SOURCE:

Merck & Co., Inc., USA PCT Int. Appl., 33 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent English

LANGUAGE:

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PA'	TENT	NO.			KIND DATE						ICAT		DATE				
WO	2005	0447	95		A1		2005	0519	,	WO 2	004-		20041025				
	W: AE, AG, AL				AM,	ΑT,	AU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	ΒZ,	CA,	CH,
		CN,	co,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,
		GE,	GH,	GM,	HR,	ΗU,	ID,	IL,	IN,	IS,	JP,	ΚE,	KG,	ΚP,	KR,	ΚZ,	LC,
		LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	ΜZ,	NA,	NI,
		NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,
		ТJ,	TM,	TN,	TR,	TT,	ΤZ,	UA,	UG,	US,	UZ,	VC,	VN,	YU,	ZA,	ZM,	ZW
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							GR,	-		-						-	
					BF,	ВJ,	CF,	CG,	CI,	CM,	GΑ,	GN,	GQ,	G₩,	ML,	MR,	ΝE,
			TD,												_		
	2004																
	2543																
EP	1682																
	R:						ES,							NL,	SE,	MC,	PT,
							TR,								_		
BR	2004 2007	0158	62		A		2007	0109		BR 2	004-	1586	2		21	0041	025
JP	2007	5099	44		T		2007	0419	1	JP 2	006-	5381	49		21		
	2006															0060	
US	2007	1354	/5		ΑI		2007	0614	US 2006-577587 US 2003-514754P							0060	
PRIORIT	Y APP	LN.	INFO	. :													
OMUED C	^!!D	/C)			C 2 C 2		m 1 4	0 - 404			004-		w 20	0041	J25		
GI GI	JURCE	(S):			CAS	REAC	T 14	2:482	2029; MARPAT 142:482029								

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

The present invention provides an efficient synthesis for the preparation of AB [(1R,3S)-3-isopropyl-3-[[3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl]carbonyl]cyclopentyl][(3S,4S)-3-methoxytetrahydro-2H-pyran-4yl]amine (I) and its succinate salt. The present invention addnl. provides an efficient syntheses for the preparation of intermediates, i.e. (3R) -3-methoxytetrahydro-4H-pyran-4-one (II), (1S, 4S) -4-(2, 5-dimethyl-1Hpyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid (III), and 3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (IV), and for the preparation of the precursor (3S, 4S) - N - ((1S, 4S) - 4 - isopropyl - 4 - [(3 - isopropyl - 4 - (3 - isopropyl(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl]carbonyl]cyclopent-2-en-1-yl)-3-methoxytetrahydro-2H-pyran-4-amine (V). The invention addnl. resides in the superior properties of the I succinate. Thus, 730 g III was treated with 228 mL methanesulfonyl chloride in the presence of 0.93 L diisopropylethylamine in $6.6\ L$ THF at $0\text{--}13^\circ$, stirred at room temperature for 4 h, cooled to .apprx.15°, treated with IV.HCl, warmed to 23°, treated with 0.93 L diisopropylethylamine with cooling at .apprx.25° over 15 min, and aged for .apprx.1 h to give 1.055 kg the compound (VI). VI (1.055 kg) in MeOH was added to 1 kg hydroxylamine hydrochloride, 50% aqueous hydroxylamine (1 L), and 5 L H2O, and the resulting slurry was refluxed at 71° for 6 h to give, after treatment with anhydrous HCl in isopropanol, the amine dihydrochloride (VII) (0.76 kg). VII (777 g) was slurried in 3 L iso-Pr acetate and the mixture was cooled in an ice bath, successively treated with 860 mL n-Bu3N, 260 mL isopropanol, and sodium triacetoxyborohydride (724 g, at 5°), and after 1 h, treated with a solution of II in iso-Pr acetate (1.76 L of a 160 g/L solution), and allowed to react for 6 h to give 654 g crude V (90%). V (640 g) was diluted with 6.4 L MeOH, charged to an autoclave, treated with a slurry of 256 g 5% Pd-C in 5.0 L MeOH, and hydrogenated under H pressure of 40 psi at 25° overnight to give a solution of 633 g I in MeOH (98.5%) which was concentrated to an oil (770 g). The oil was dissolved in 3.1 L iso-Pr acetate and the solution was concentrated to a brown oil. Dilution with iso-Pr acetate and

concentration was repeated two addnl. times. The resulting oil was converted into I benzenesulfonate (1.645 kg) by treating with 283 g benzenesulfonic acid in iso-Pr acetate and treatment with heptane and the resulting benzenesulfonate salt was treated with a mixture of K2CO3, H2O, and iso-Pr acetate to give an oil containing 1.16 kg I. The latter oil was treated with 294 g succinic acid in ethanol and heptane to give 1.328 kg I succinate. 624733-88-6P

RL: IMF (Industrial manufacture); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of

CN D-erythro-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-4-O-methyl- (CA INDEX NAME)

Absolute stereochemistry.

ΙT

IT 851916-42-2P 851916-43-3P

RL: IMF (Industrial manufacture); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of

[(1R,3S)-3-isopropyl-3-[[3-(trifluoromethyl)-7,8-dihydro-1,6naphthyridin-6(5H)-yl]carbonyl]cyclopentyl][(3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl]amine salt as chemokine receptor CCR-2 antagonist) RN 851916-42-2 CAPLUS

CN D-erythro-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-

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methylethyl)cyclopentyl]amino]-4-O-methyl-, butanedioate (1:1) (salt)
(9CI) (CA INDEX NAME)
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CM 1

CRN 624733-88-6 CMF C24 H34 F3 N3 O3

Absolute stereochemistry.

CM 2

CRN 110-15-6 CMF C4 H6 O4

 ${\tt HO_2C-CH_2-CH_2-CO_2H}$

RN 851916-43-3 CAPLUS

CN D-erythro-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-4-O-methyl-, monobenzenesulfonate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 624733-88-6 CMF C24 H34 F3 N3 O3

CM

CRN 98-11-3 CMF C6 H6 O3 S

REFERENCE COUNT:

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ANSWER 4 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN

3

ACCESSION NUMBER:

DOCUMENT NUMBER:

TITLE:

2005:426431 CAPLUS

142:482028

Preparation of [(1R,3S)-3-isopropyl-3-[[3-

(trifluoromethyl) -7,8-dihydro-1,6-naphthyridin-6(5H)yl]carbonyl]cyclopentyl][(3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl]amine salt as chemokine receptor CCR-2

antagonist

INVENTOR(S):

Jensen, Mark; Larsen, Robert; Sidler, Daniel Richard

PATENT ASSIGNEE(S): Merck & Co., Inc., USA SOURCE: PCT Int. Appl., 28 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PAT	CENT I	KIND DATE				j	APPL:	ICAT		DATE							
WO	2005	0442	64		A1	-	2005	0519	1	WO 2	004-		20041025				
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	RW:	BW,	GH,	GM,	KE,	LS,	MW,	MZ,	NA,	SD,	SL,	SZ,	TZ,	ŪĠ,	ZM,	ZW,	AM,

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AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
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      CN 1870998
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                                                                                       20060524
PRIORITY APPLN. INFO.:
                                                         US 2003-514735P
                                                                                   Ρ
                                                                                      20031027
                                                         WO 2004-US35069
                                                                                  W 20041025
                                CASREACT 142:482028
OTHER SOURCE(S):
GΙ
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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

The present invention provides an efficient synthesis for the preparation of AB [(1R,3S)-3-isopropyl-3-[[3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl]carbonyl]cyclopentyl][(3S,4S)-3-methoxytetrahydro-2H-pyran-4yl]amine (I) and its succinate salt. The present invention addnl. provides an efficient syntheses for the preparation of intermediates, i.e. (3R) -3-methoxytetrahydro-4H-pyran-4-one (II), (1S, 4S) -4-(2, 5-dimethyl-1Hpyrrol-1-yl)-1-isopropylcyclopent-2-ene-1-carboxylic acid (III), and 3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (IV), and for the preparation of the precursor (3S, 4S)-N-((1S, 4S)-4-isopropyl-4-[[3-isopropyl-4-[3-isopropyl-4(trifluoromethyl) -7,8-dihydro-1,6-naphthyridin-6(5H)-yl]carbonyl]cyclopent-2-en-1-y1)-3-methoxytetrahydro-2H-pyran-4-amine (V). The invention addnl. resides in the superior properties of the I succinate. I succinate is useful for treating, ameliorating, controlling or reducing the risk of an inflammatory and immunoregulatory disorder or disease or rheumatoid arthritis. Thus, 730 g III was treated with 228 mL methanesulfonyl chloride in the presence of 0.93 L diisopropylethylamine in 6.6 L THF at 0-13°, stirred at room temperature for 4 h, cooled to .apprx.15°, treated with IV.HCl, warmed to 23° , treated with 0.93 L diisopropylethylamine with cooling at .apprx.25° over 15 min, and aged for .apprx.1 h to give 1.055 kg the compound (VI). VI (1.055 kg) in MeOH was added to 1 kg hydroxylamine hydrochloride, 50% aqueous hydroxylamine (1 L), and 5 L H2O, and the resulting slurry was refluxed at 71° for 6 h to give, after treatment with anhydrous HCl in isopropanol, the amine dihydrochloride (VII) (0.76 kg). VII (777 g) was slurried in 3 L iso-Pr acetate and the mixture was cooled in an ice bath, successively treated with 860 mL n-Bu3N, 260 mL isopropanol, and sodium triacetoxyborohydride (724 g, at 5°), and after 1 h, treated with a solution of II in iso-Pr acetate (1.76 L of a 160 g/L solution), and allowed to react for 6 h to give 654 g crude V (90%). V (640 g) was diluted with 6.4 L MeOH, charged to an autoclave, treated with a slurry of 256 g 5% Pd-C in 5.0 L MeOH, and hydrogenated under H pressure of 40 psi at 25° overnight to give a solution of 633 g I in MeOH (98.5%) which was concentrated to an oil (770 g).

The

oil was dissolved in 3.1 L iso-Pr acetate and the solution was concentrated to

brown oil. Dilution with iso-Pr acetate and concentration was repeated two addnl.

times. The resulting oil was converted into I benzenesulfonate (1.645 kg) by treating with 283 g benzenesulfonic acid in iso-Pr acetate and

treatment with heptane and the resulting benzenesulfonate salt was treated with a mixture of K2CO3, H2O, and iso-Pr acetate to give an oil containing 1.16 kg I. The latter oil was treated with 294 g succinic acid in ethanol and heptane to give 1.328 kg I succinate. ΙT 624733-88-6P RL: IMF (Industrial manufacture); PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses) (preparation of [(1R, 3S)-3-isopropyl-3-[[3-(trifluoromethyl)-7, 8-dihydro-1, 6-isopropyl-3-[[3-(trifluoromethyl)-7, 8-isopropyl-3-[[3-(trifluoromethyl)-7, 8-isopropyl-3-[[3-(trifluoromethyl)-7, 8-isopropyl-3-[[3-(trifluoromethyl)-7, 8-isopropyl-3-[[3-(trifluoromethyl)-7, 8-isopropyl-3-[[3-(trifluoromethyl)-7, 8-isopropyl-3-[[3-(trifluoromethyl]-3-[[3-(trifluoromethyl]-3-[[3-(trifluoromethyl]-3-[[3-(trifluoromethyl]-3-[[3-(trifluoromethyl]-3-[[3-(trifluoromethyl]-3-[[3-(trifluoromethyl]-3-[[3-(trifluoromethyl]-3-[[3-(trifluoromethyl]-3-[[3-(trifluoromethyl]-3-[[3-(trifluoromethyl]-3-[[3-(trifluoromethyl]-3-[[3-(trifluoromethyl]-3-[[3-(trifluoromethnaphthyridin-6(5H)-yl]carbonyl]cyclopentyl][(3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl]amine salt as chemokine receptor CCR-2 antagonist) RN 624733-88-6 CAPLUS CN D-erythro-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl) - 1, 6-naphthyridin - 6(5H) - y1] carbonyl] - 3 - (1methylethyl)cyclopentyl]amino]-4-O-methyl- (CA INDEX NAME)

Absolute stereochemistry.

Absolute stereochemistry.

IT 851916-42-2P 851916-43-3P RL: IMF (Industrial manufacture); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of [(1R,3S)-3-isopropyl-3-[[3-(trifluoromethyl)-7,8-dihydro-1,6-isopropyl-3-[[3-(trifluoromethyl)-3-[[3-(trifluoromethyl)-3-[[3-(trifluoromethyl]-3-[[3-(trifluoromethyl)-3-[[3-(trifluoromethyl)-3-[[3-(trifluoromethyl)-3-[[3-(trifluoromethyl]-3-[[3-(trifluoromethyl)-3-[[3-(trifluoromethyl]-3-[[3naphthyridin-6(5H)-yl]carbonyl]cyclopentyl][(3S,4S)-3-methoxytetrahydro-2H-pyran-4-yl]amine salt as chemokine receptor CCR-2 antagonist) RN 851916-42-2 CAPLUS CN D-erythro-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1methylethyl)cyclopentyl]amino]-4-O-methyl-, butanedioate (1:1) (salt) (9CI) (CA INDEX NAME) CM 1 CRN 624733-88-6 CMF C24 H34 F3 N3 O3

CM 2

CRN 110-15-6 CMF C4 H6 O4

 ${\tt HO_2C-CH_2-CH_2-CO_2H}$

RN 851916-43-3 CAPLUS

CN D-erythro-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-4-O-methyl-, monobenzenesulfonate (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 624733-88-6 CMF C24 H34 F3 N3 O3

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:1124588 CAPLUS

DOCUMENT NUMBER: 142:69197

TITLE: CCR-2 antagonists for treatment of neuropathic pain

INVENTOR(S): Abbadie, Catherine; Lindia, Jill Ann; Wang, Hao

PATENT ASSIGNEE(S): Merck & Co., Inc., USA SOURCE: PCT Int. Appl., 304 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.						D	DATE			APPL	ICAT	DATE					
						-											
· · ·	2004		. •		A2		2004		1	WO 2	004-		2	0040	602		
WO	2004	04110376			A3 20050			0224	1								
	W:	AE,	AG,	AL,	AM,	AT,	ΑU,	ΑZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,
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US		A1		2006	0914	1	US 2	005-	5597	01		20	0051	206			
PRIORITY	.:					1	US 2	003-	4763	91P		P 20	0030	606			
						1	US 2	003-	5316	37P		P 20	00312	222			
									1	WO 2	004-1	US17	499	1	W 20	0040	602
OWHER COURCE (C).					MAD	ת ע כו	142.	60101	7								

OTHER SOURCE(S): MARPAT 142:69197

AB The invention is directed to methods of treating neuropathic pain and other neuropathic diseases and conditions with CCR-2 antagonists and pharmaceutical composition containing CCR-2 antagonists.

IT 625097-60-1P 625097-61-2P 625097-62-3P

625097-63-4P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(CCR2 antagonists for treatment of neuropathic pain)

RN 625097-60-1 CAPLUS

CN D-erythro-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(2,2,2-trifluoroethyl)cyclopentyl]amino]-4-O-methyl- (CA INDEX NAME)

RN 625097-61-2 CAPLUS

CN D-erythro-Pentitol, 1,5-anhydro-3,4-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(2,2,2-trifluoroethyl)cyclopentyl]amino]-2-O-methyl- (CA INDEX NAME)

Absolute stereochemistry.

RN 625097-62-3 CAPLUS

CN L-threo-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(2,2,2-trifluoroethyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 625097-63-4 CAPLUS

CN D-threo-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(2,2,2-trifluoroethyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2003:892775 CAPLUS DOCUMENT NUMBER: 139:381471

TITLE: 139:3814

Preparat

Preparation of tetrahydropyranyl cyclopentyl tetrahydropyridopyridines as modulators of chemokine

receptor activity

INVENTOR(S):

SOURCE: \

Jiao, Richard; Morriello, Gregori; Yang, Lihu; Moyes,

Christopher

PATENT ASSIGNEE(S):

Merck & Co., Inc., USA; Merck Sharp & Dohme Limited

PCT Int. Appl., 52 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

	PATENT NO.							DATE			APP	LICAT		DATE						
	WO	2003	0932	66		A1	-	2003	1113		 WO	2003-		20030425						
		W:	ΑE,	AG,	AL,	AM,	AT,	ΑU,	ΑZ,	BA,	BB	, BG,	BR,	BY,	BZ,	CA,	CH,	CN,		
			CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC	, EE,	ES,	FI,	GB,	GD,	GE,	GH,		
			GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE	, KG,	KR,	ΚZ,	LC;	LK,	LR,	LS,		
	LT, LU, LV,					MA,	MD,	MG,	MK,	MN,	MW	, MX,	MZ,	NI,	NO,	ΝZ,	OM,	PH,		
	PL, PT, RO,					RU,	SC,	SD,	SE,	SG,	SK	, SL,	TJ,	TM,	TN,	TR,	TT,	ΤZ,		
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		22850				C2		2006				2004-					0030			
		2005						2005				2004-8					0040			
		20040				A		2007				2004-0	-	_		_	0041			
		20041				A		2005				2004-1					0041			
NO 2004005235						А		2004	1129			2004-				_	0041:			
PRIORITY APPLN. INFO.:												2002-3					0020			
											WO	2003-	72.T3	042	,	N 2	0030	425		

OTHER SOURCE(S):

MARPAT 139:381471

GΙ

AB Title compds. I (R1 = H, F, OH, alkoxy, or alkyl optionally substituted with 1-6 fluoro atoms; R2 = O or absent) and their pharmaceutically acceptable salts are prepared and disclosed as modulators of chemokine receptor activity. Thus, II was prepared by condensation of tetrahydro-4H-pyran-4-one with the corresponding aminocyclopentane precursor (preparation given). In particular, these compds. are useful as

Ι

modulators of the chemokine receptor CCR-2. I was found generally to possess an IC50 value of less than about 1 μ M in binding to the CCR-2 receptor in performed assays. IT 624733-87-5P 624733-88-6P 624733-89-7P 624733-90-0P 624734-12-9P 624734-13-0P 624734-14-1P 624734-15-2P RL: PAC (Pharmacological activity); PUR (Purification or recovery); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of tetrahydropyranyl cyclopentyl tetrahydropyridopyridines as modulators of chemokine receptor activity) RN 624733-87-5 CAPLUS CN D-erythro-Pentitol, 1,5-anhydro-3,4-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1methylethyl)cyclopentyl]amino]-2-O-methyl- (CA INDEX NAME)

Absolute stereochemistry.

RN 624733-88-6 CAPLUS
CN D-erythro-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-4-O-methyl- (CA INDEX NAME)

Absolute stereochemistry.

RN 624733-89-7 CAPLUS · D-threo-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-

(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1methylethyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 624733-90-0 CAPLUS

CN L-threo-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 624734-12-9 CAPLUS

CN D-erythro-Pentitol, 1,5-anhydro-3,4-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-1-oxido-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-2-O-methyl- (CA INDEX NAME)

RN 624734-13-0 CAPLUS

CN D-erythro-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-1-oxido-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-4-O-methyl- (CA INDEX NAME)

Absolute stereochemistry.

RN 624734-14-1 CAPLUS

CN D-threo-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-1-oxido-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

RN 624734-15-2 CAPLUS

CN L-threo-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-1-oxido-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-4-0-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT:

3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 7. CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2003:892537 CAPLUS

DOCUMENT NUMBER:

139:381470

TITLE:

Preparation of tetrahydropyranyl cyclopentyl

tetrahydropyridopyridine as modulators of chemokine

receptor activity

INVENTOR(S):

Jiao, Richard; Morriello, Gregori; Yang, Lihu; Goble, Stephen D.; Mills, Sander G.; Pasternak, Alexander;

Zhou, Changyou; Butora, Gabor; Kothandaraman,

Shankaran; Guiadeen, Deodialsingh; Tang, Cheng; Moyes,

Christopher

PATENT ASSIGNEE(S):

Merck & Co., Inc., USA; Merck Sharp & Dohme Limited

SOURCE: PCT Int. Appl., 207 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent English

LANGUAGE: FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE ____ WO 2003092586 Α2 20031113 WO 2003-US12929 20030425 WO 2003092586 A3 20040916 AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, PL, PT, RO, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG KG, KZ, MD, FI, FR, GB, BF, BJ, CF, CA 2483752 20031113 CA 2003-2483752 **A1** 20030425 AU 2003231114 20031117 AU 2003-231114 A1 20030425 EP 1501507 A2 20050202 EP 2003-724241 20030425 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK NZ 536477 Α 20050527 NZ 2003-536477 20030425 JP 2005523929 Т 20050811 JP 2004-500771 20030425 JP 3780291 В2 20060531 20060628 ZA 2004007940 Α 'ZA 2004-7940 20041001 PRIORITY APPLN. INFO.: US 2002-376180P Ρ 20020429 WO 2003-US12929 W 20030425 OTHER SOURCE(S): MARPAT 139:381470 GΙ

AB Title compds. I (X = O, S, SO2, CR11R12, etc.; R1 = OH, (un)substituted alkyl, alkyloxyalkyl, Ph, heterocycle, etc.; , R2 = H, OH, halo, CN, heterocycle, (un)substituted alkyl, etc.; R3 = O or absent; R4 H, alkyl, F3C, F3CO, Cl, Br, F, and Ph; R5 = F, Cl, Br, CN, (un)substituted alkyl, thioalkyl, etc.; R6 = H, alkyl, F3C, F, Cl, Br; R7 = H, (un)substituted

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alkyl; R8 = H, OH, F, (un)substituted alkyl, or R7 and R8 may joined to from a carbocycle or heterocycle, etc.; R9 = H, OH, (un)substituted alkyl, alkyloxy, carboxylate, or R8 and R9 may together from a carbocycle or heterocycle, etc.; R10 = H, F, cycloalkyloxy, (un)substituted alkyloxy, alkyl, or R8 and R10 may together form a 5-6 membered (un)substituted ring; R11 and R12 = independently H, OH, (un)substituted alkyl, benzyl, cycloalkyl, etc.; n = 0-2) and their pharmaceutically acceptable salts were prepared and disclosed as modulators of chemokine receptor activity. Thus, II was prepared by condensation of tetrahydro-4H-pyran-4-one with the corresponding amino cyclopentyl precursor (preparation given). In particular, these compds. are useful as modulators of the chemokine receptor CCR-2. I had activity in binding to the CCR-2 receptor generally with an IC50 of less than about 1 μ M.

IT 625097-14-5P 625097-40-7P 625097-89-4P

RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

(claimed compound; preparation of tetrahydropyranyl cyclopentyl tetrahydropyridopyridines as modulators of chemokine receptor activity)

RN 625097-14-5 CAPLUS

CN

Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-4-0-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 625097-40-7 CAPLUS

CN Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-1-oxido-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

RN 625097-89-4 CAPLUS

CN Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3R)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(3,3,3-trifluoropropyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

IT 624733-87-5P 624733-88-6P 624733-89-7P 624734-12-9P 624734-13-0P 624734-14-1P 624734-15-2P

RL: PAC (Pharmacological activity); PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(claimed compound; preparation of tetrahydropyranyl cyclopentyl tetrahydropyridopyridines as modulators of chemokine receptor activity) 624733-87-5 CAPLUS

D-erythro-Pentitol, 1,5-anhydro-3,4-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-2-O-methyl- (CA INDEX NAME)

Absolute stereochemistry.

RN

CN

RN 624733-88-6 CAPLUS

CN D-erythro-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-4-O-methyl- (CA INDEX NAME)

Absolute stereochemistry.

RN 624733-89-7 CAPLUS

CN D-threo-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

RN 624734-12-9 CAPLUS

CN D-erythro-Pentitol, 1,5-anhydro-3,4-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-1-oxido-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-2-O-methyl- (CA INDEX NAME)

Absolute stereochemistry.

RN 624734-13-0 CAPLUS

CN D-erythro-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-1-oxido-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-4-O-methyl- (CA INDEX NAME)

RN 624734-14-1 CAPLUS

CN D-threo-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-1-oxido-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 624734-15-2 CAPLUS

CN L-threo-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-1-oxido-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1-methylethyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

IT 624733-90-0P 625097-60-1P 625097-61-2P
625097-62-3P 625097-63-4P 625097-90-7P
625097-91-8P 625097-92-9P 625097-93-0P
RL: PAC (Pharmacological activity); PUR (Purification or recovery); SPN
(Synthetic preparation); THU (Therapeutic use); BIOL (Biological study);
PREP (Preparation); USES (Uses)
(claimed compound; preparation of tetrahydropyranyl cyclopentyl
tetrahydropyridopyridines as modulators of chemokine receptor activity)
RN 624733-90-0 CAPLUS
CN L-threo-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(1methylethyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 625097-60-1 CAPLUS
CN D-erythro-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(2,2,2-trifluoroethyl)cyclopentyl]amino]-4-O-methyl- (CA INDEX NAME)

RN 625097-61-2 CAPLUS

CN D-erythro-Pentitol, 1,5-anhydro-3,4-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(2,2,2-trifluoroethyl)cyclopentyl]amino]-2-O-methyl- (CA INDEX NAME)

Absolute stereochemistry.

RN 625097-62-3 CAPLUS

CN L-threo-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(2,2,2-trifluoroethyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 625097-63-4 CAPLUS

CN D-threo-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3S)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(2,2,2-trifluoroethyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 625097-90-7 CAPLUS

CN D-erythro-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3R)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(3,3,3-trifluoropropyl)cyclopentyl]amino]-4-O-methyl- (CA INDEX NAME)

RN 625097-91-8 CAPLUS

CN D-erythro-Pentitol, 1,5-anhydro-3,4-dideoxy-3-[[(1R,3R)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(3,3,3-trifluoropropyl)cyclopentyl]amino]-2-O-methyl- (CA INDEX NAME)

Absolute stereochemistry.

RN 625097-92-9 CAPLUS

CN L-threo-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3R)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(3,3,3-trifluoropropyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 625097-93-0 CAPLUS

CN D-threo-Pentitol, 1,5-anhydro-2,3-dideoxy-3-[[(1R,3R)-3-[[7,8-dihydro-3-(trifluoromethyl)-1,6-naphthyridin-6(5H)-yl]carbonyl]-3-(3,3,3-trifluoropropyl)cyclopentyl]amino]-4-O-methyl- (9CI) (CA INDEX NAME)

(FILE 'HOME' ENTERED AT 08:31:35 ON 20 NOV 2007)

FILE 'REGISTRY' ENTERED AT 08:31:54 ON 20 NOV 2007

L1 STRUCTURE UPLOADED

L2 6 S L1

L3 84 S L1 FULL

FILE 'CAPLUS' ENTERED AT 08:32:26 ON 20 NOV 2007

L4 7 S L3/PREP FULL

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COST IN U.S. DOLLARS

SINCE FILE TOTAL
ENTRY SESSION
FULL ESTIMATED COST

40.78
213.09

OBE ESTIMATED COST 40.70 ZIS.05

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)
SINCE FILE TOTAL ENTRY SESSION

CA SUBSCRIBER PRICE -5.46 -5.46

STN INTERNATIONAL LOGOFF AT 08:35:04 ON 20 NOV 2007